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09/412,268	10/05/1999	BEHNAZ PARHAMI-SEREN	MGH-1526	9455

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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/412,268	Parhami-Seren et al
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 30, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above, claim(s) *7-37* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-6, 38, and 39* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *7,9*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

1. The Election filed January 30, 2002 (Paper No. 11) in response to the Office Action of October 2, 2001 (Paper No.1) is acknowledged and has been entered. Claim 39 has been added. Claims 1-39 are pending in the application and Claims 7-37 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-6, 38-39 are currently under prosecution.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

3. Claims 2, 5, 6 are rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility.

The claims are drawn to antibody 5A12, 1-10, 8E4, 7-1 wherein said antibody binds ouabain but does not crossreact with digoxin. The specification teaches that antibody 5A12 cross reacts with digoxin (see p. 22, line 19 and Figure 3). Further, although the specification teaches that antibody 1-10 and 8E4 do not cross react with digoxin, a review of Figure 6 reveals that at 70 uM concentration of digoxin, both the binding of antibody 1-10 and antibody 8E4 to Oua-BGG are inhibited by digoxin and therefore the each antibody is cross reacting with the digoxin. Further, as drawn to antibody 7-1, although the specification states that there is no cross-reactivity of the antibody with digoxin at 100 uM concentration, (see Table I), the specification states that the activity of antibody 7-1 and 1-10 are

essentially identical and given the cross-reactivity found at 70 uM for monoclonal antibody 1-10, it is expected that monoclonal antibody 7-1 also cross reacts with digoxin at that concentraiton. The claimed embodiments are inoperative and therefore do not have utility.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

5. Claims 2, 5, 6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The claims are drawn to antibody 5A12, 8E4, 7-1, 1-10 wherein said antibody binds ouabain but does not crossreact with digoxin. The specification teaches as set forth above. Since the embodiments are inoperative, one of skill in the art would not know how to use the claimed invention with a reasonable expectation of success.

6. The specification is objected to and claims 2, 5, 6 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the

specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

The claim is drawn to monoclonal antibodies 1-10, 5A12, 7-1, 8E4 and antigen binding fragments thereof.

It is unclear if a cell line which produces an antibody having the exact structural and chemical identity of 1-10, 5A12, 7-1, 8E4 and antigen binding fragments thereof is known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to a hybridoma cell line producing monoclonal antibody 1-10, 5A12, 7-1, 8E4 and antigen binding fragments thereof, it would not be possible to practice the claimed invention. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be

folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species, 1-10, 5A12, 7-1, 8E4 and antigen binding fragments thereof. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Applicant's referral to the deposit of the cell lines wherein no deposit numbers are included on page 8 of the specification is an insufficient assurance that all required deposits have been made and all the conditions of MPEP 608.01 (p)(c) met.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

Affidavits and declarations, such as those under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application

Amendment of the specification to recite the deposit numbers is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of the deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

7. Claims 1, 3, 4, 38, 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at

the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth antibody species, 1-10, 5A12, 7-1, 8E4 and therefore the written description is not commensurate in scope with the claims drawn to antibodies that bind to ouabain but do not crossreact with digoxin.

Although the specification claims antibodies that bind ouabain and do not cross react with digoxin, and specifically states that the specific antibodies claimed and exemplified do not cross react with digoxin, the data presented in the specification clearly shows that the antibodies exemplified do minimally cross react with digoxin. The instant disclosure of these cross reacting species of antibodies does not adequately describe the scope of the claimed genus, which encompasses all antibodies that do not cross react with digoxin. Although drawn to the DNA art, the findings of the court in *Regents of the University of California v. Eli Lilly &* is clearly relevant to the instant rejection. A description of a genus of cDNAs may be acheived by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural freatures common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant disclosure does not describe a single monoclonal antibody that does not cross react with digoxin. One of skill in the art would reasonably conclude that the inventor(s), at the time the application was filed, did not have possession of the claimed invention.

8.. Claims 2, 5 and 6 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 5 and 6 are indefinite in the recitation of antibodies 1-10, 5A12, 7-1, 8E4 as the sole means of identifying the claimed antibodies. The use of laboratory designations only to identify a particular antibody/cell line renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct hybridomas and antibodies. Amendment of the claims to include the depository accession number of the mAb or hybridoma is required, because deposit accession numbers are unique identifiers which unambiguously define a given hybridoma and/or monoclonal antibody.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 3, 4, 39 are rejected under 35 U.S.C. § 102(b) as being anticipated by Lin et al, PNAS, ROC Part B: Life Sciences, 1998, 22:129-134, IDS item.

It is noted, as drawn to claim 39, that the production of a product by a particular process does not impart novelty or unobviousnes to a product when the same product is taught by the prior art. See In re Thorpe, 227 USPQ 964 (CAFC

1985); In re Marosi, 218 USPQ 289, 292-293 (CAFC 1983); In re Brown, 173 USPQ 685 (CCPA 1972).

The claims are drawn to a monoclonal antibody or antigen binding fragment thereof having binding affinity for ouabain, wherein the antibody or antigen binding fragment does not crossreact with digoxin, said antibody produced by a particular process, wherein the binding affinity constant for ouabain is at least about 2×10^{-8} M, at least about $3 +/- 1 \times 10^{-7}$ M.

Lin et al teach a monoclonal antibody with binding affinity for ouabain wherein the antibody specifically and selectively binds ouabain (p. 131, cols 1 and 2) in human serum sample (p.132, col 2), wherein the presence of ouabain in human serum is demonstrated. Lin et al make clear the separability of ouabain and digoxin assays wherein they teach an antibody and immunoassay to digoxin in human serum, wherein it is demonstrated that human serum contains endogenous digoxin (p.132, col 1 and p. 133, col 1). Although the reference does not specifically teach that the ouabain monoclonal antibodies do not crossreact with digoxin and that they have the binding affinities as claimed, the claimed antibodies appears to be the same as the prior art antibodies, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from that taught by the prior art and to establish

patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

12. Claims 1, 3, 4, 38, 39 are rejected under 35 U.S.C. § 103 as being unpatentable over US Patent No. 5,164,296, IDS item in view of Lin et al, Supra, and Blaustein, (Kidney Int'l, 1996, 49:1748-1753, IDS item).

It is noted, as drawn to claim 39, that the production of a product by a particular process does not impart novelty or unobviousnes to a product when the same product is taught by the prior art. See In re Thorpe, 227 USPQ 964 (CAFC 1985); In re Marosi, 218 USPQ 289, 292-293 (CAFC 1983); In re Brown, 173 USPQ 685 (CCPA 1972).

The claims are drawn to a monoclonal antibody or antigen binding fragment thereof having binding affinity for ouabain, wherein the antibody or antigen binding fragment does not crossreact with digoxin, wherein said antibody is in a pharmaceutical composition, said antibody produced by a particular process, wherein the binding affinity constant for ouabain is at least about 2×10^{-8} M, at least about $3 +/- 1 \times 10^{-7}$ M.

US Patent No. 5,164,296 teaches an antibody having specificity for ouabain (col 7, lines 50-51). An antibody having binding specificity for ouabain means an antibody which has high affinity for ouabain, i.e. a dissociation constant on the order of about 7.0 nM or less for ouabain, generally 0.5 to 7.0 nM of ouabain typically about 5.0 nM of ouabain and low cross reactivity for the well-known steroids present in human plasma on the order of about 1.0% or less cross reactivity, typically 0.02 to 0.001% cross reactivity. The antibody can be monoclonal (col 14, lines 20-32). Further, assay conditions that optimize the assay for sensitivity and minimize the errors that may result from the assay of body fluids and tissue samples

of slightly varying composition are preferred (col 14, lines 59-63). US Patent No. 5,164,296 also reaches a method for diagnosing hypertension using said antibody comprising obtaining a body fluid or tissue sample from a subject with high blood pressure, using said antibody to immunologically measure the level of human ouabain in the body fluid, comparing the level to a ouabain standard to detect a normal or elevated level of human ouabain to diagnose the presence or absence of hypertension (col 7, lines 16-17 and col 8, lines 1-16), a method for monitoring hypertension using said antibody (col 9, lines 55-col 10, line 4) and a method of treating hypertension using said antibody (col 11 lines 1-6) by intravenous infusion (col 16, lines 9-10) wherein the antibody is inherently in a pharmaceutical composition. US Patent No. 5,164,296 further teaches that the polyclonal antisera to ouabain was tested to determine the degree to which it cross-reacted with other substances known to be present in human body fluids and tissues as well as cardiotonic steroids closely related to ouabain but not known to be present in human body tissues and fluids. It was determined that the polyclonal antibodies cross reacted with digoxin, 5.2%, a cardiotonic steroid not known at the time the invention was made, to be present in human body fluids and tissues. US Patent No. 5,164,296 teaches as set forth above but does not teach an antibody that does not crossreact with digoxin.

Lin et al teach as set forth previously, in particular the presence of endogenoujs digoxin in human serum is noted.

Blaustein teaches that elevated levels of endogenous ouabain play a central role in the pathogenesis of hypertension (see Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of US Patent No.5,164,296 to screen the monoclonal antibodies of US Patent No. 5,164,296 for antibodies that do not cross react with digoxin because US Patent No. 5,164,296 specifically teaches that the antibodies of the invention are useful for diagnosing and monitoring hypertension in human tissues and fluids and specifically teaches that the antibodies must have low cross-reactivity, that is on the order of 1.0% or less cross-reactivity which reads on no cross reactivity and because Blaustein teaches that elevated levels of endogenous ouabain play a central role in the pathogenesis of hypertension and because US Patent No. 5,164,296 specifically teaches that at the time the invention was made that it was not known that digoxin was present in human body fluids and tissues while Lin et al later teach that digoxin is present in human fluids and tissues. Further, US Patent No. 5,164,296 specifically teaches that optimization of the assays is preferred and it is clear that one of skill in the art would want to optimize the assay, given the teachings of Lin et al, in order to eliminate artifactural binding to endogenous digoxin. One would have been motivated to screen for monoclonal antibodies that do not cross react with digoxin in order to distinguish between the cross reacting digoxin and endogenous ouabain in order to optimize the assays and the accurate diagnosis and monitoring of hypertension in human sugjects.

13. No claims allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is

(703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
April 5, 2002